## REMARKS

The instant Office Action mailed July 8, 2004, set a three-month shortened statutory period for response expiring October 8, 2004. Pursuant to the Petition for Extension of Time under 37 C.F.R. 1.136(a) submitted herewith, the period for response is extended three months to January 8, 2005. This amendment is therefore timely filed.

Claims 1-10 were in the application as originally filed. Claims 1-10 were cancelled and Claims 11-18 were added in the Preliminary Amendment filed on November 2, 2001. Claims 19-26 are added above. Claims 11-26 are in the application.

Claims 11, 12, 15 and 16 have been amended in order to indicate that the compounds are administered to the patient undergoing chronic, intermittent, extracorporeal blood treatment. Support for these amendments can be found, for example, on page 3, lines 1-7 of the specification.

New Claims 19-26 are directed to methods wherein the compounds are administered to the extracorporeal blood circuit and which correspond to Claims 11-18, differing only as to the site of administration. Support for these claims can be found, for example, on page 3, lines 1-20 of the specification.

Claims 11-18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the stated reason that the phrase "administering for each treatment" renders the claims indefinite, because it is not clear to whom or what the compounds are administered.

This rejection is believed overcome and should be withdrawn in view of the amendments to Claims 11, 12, 15 and 16, and also with respect to new Claims 19-26, for which it is specified to whom or to what the compounds are administered, i.e. to the patient undergoing chronic, intermittent, extracorporeal blood treatment, or to the extracorporeal blood circuit itself.

Claims 11-18 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kudo et al. (U.S. Patent No. 4,331,697), in view of Ahmad et al. (U.S. Patent No. 5,252,213) and further in view of Petitou et al. (U.S. Patent No. 5,378,829) on the grounds that Kudo et al. generally teach that extracorporeal circuits cause blood clotting upon contact with the blood of a patient, and the blood clotting is prevented by the administration of an anti-coagulant; that Ahmad et al. generally teach that patients suffering from renal failure undergo chronic, intermittent extracorporeal blood circuit treatment, and thrombus formation in dialysis machines is prevented by the addition of

anticoagulants; and that Petitou et al. disclose the pentasaccharides of instant Claims 11-18, and teach that the compounds have antithrombin and antithrombotic activity, and can be administered enterally or parenterally, in a daily dose of 0.001-10 mg per kg body weight.

This rejection is traversed and reconsideration and withdrawal thereof are respectfully requested for the reasons given hereinbelow.

The instant invention is directed to methods for preventing clotting induced by contact with surfaces in an extracorporeal blood circuit for a patient undergoing chronic, intermittent, extracorporeal blood treatment comprising administering a certain dosage of a synthetic oligosaccharide. The synthetic oligosaccharides of the instant invention highly and selectively inhibit factor Xa via anti-thrombin III (ATIII), yet have no activity on thrombin (specification, p. 1). Surprisingly, though, Applicants have discovered that the compounds inhibit thrombin formation in extracorporeal blood circuits.

The primary reference cited by the Examiner, Kudo et al., teaches methods of making medical devices antithrombotic by treating the surfaces of the devices with certain heparin derivatives. Kudo et al. also maintain that it is conventional to systemically administer an antithrombotic agent, such as heparin, coumarin, sodium citrate, et cetera, to prevent thrombus formation in biomedical materials, but assert that such systemic administration has the defect of causing a marked danger of bleeding, thereby teaching away from such systemic administration. Kudo et al. fail to teach the required dosage of any antithrombotic agent which would prevent clotting in an extracorporeal blood circuit. Additionally, as acknowledged by the Examiner, Kudo et al. do not teach or suggest the use of any synthetic oligosaccharides, let alone those of the instant invention, to prevent such clotting, nor do Kudo et al. describe intermittent extracorporeal blood treatment, all of which are required by Applicants' claims.

Apparently recognizing the above-mentioned deficiencies in the primary Kudo et al. reference, the Examiner relies on the Ahmad et al. patent stating that the reference teaches that thrombus formation in dialysis machines for patients undergoing extracorporeal blood circuit treatment is prevented by the addition of anticoagulant agents, such as heparin derivatives. Initially, Applicants note that Ahmad et al. does not describe any systemic treatment with anticoagulants for prevention of clotting in an extracorporeal blood circuit, and thus does not teach or suggest administration of an anticoagulant to a patient undergoing such intermittent treatment, as is required by Claims 11-18. Moreover, Ahmad et al. do not teach or suggest the use of the synthetic

oligosaccharides of the instant invention in preventing thrombus formation in dialysis machines, nor do Ahmad et al. in any way suggest the dosage required of any anticoagulant that would result in such prevention, all of which are required by the instantly rejected claims.

Lastly, the Petitou et al. disclosure describes compounds taught to be useful as thrombus generation inhibitors and as inhibitors of smooth muscle cell proliferation. Petitou et al. teach a daily dosage of 0.001 to 10 mg per kg of a compound of the invention *for the treatment of venous thrombosis or for the inhibition of smooth muscle cell proliferations*. Petitou et al. do not teach or suggest the use of any compound to prevent clotting in an extracorporeal blood circuit, and additionally fail to teach or suggest the necessary dosage for such use. The Examiner, however, maintains that the daily dosage for the treatment of venous thrombosis or for the inhibition of smooth muscle cell proliferation is identical to the dosage per treatment instantly claimed. Nevertheless, absent the hindsight benefit of Applicants' disclosure, nothing in any of the references cited by the Examiner would have suggested that a similar dosage useful for the treatment of venous thrombosis or for the inhibition of smooth muscle cell proliferation would be useful for preventing clotting in an extracorporeal blood circuit. Thus, at most, the combination of the three references cited by the Examiner might make it obvious to try the claimed compounds at the same dosage taught by Petitou et al. for the daily treatment of venous thrombosis in order to prevent clotting in extracorporeal blood circuit. However, it is well settled that "obvious to try" is not the standard against which obviousness is measured under 35 U.S.C. § 103. *In re Goodwin 198 USPQ 1; In re Antonie 195 USPQ 6.*

Thus, given that Kudo et al. teach away from systemic treatment of an antithrombotic compound to prevent clotting upon contact with a biomedical material, that Ahmad et al. fail to describe any systemic treatment of an antithrombotic compound, and that Petitou et al. do not teach or suggest the use of the claimed compounds to prevent clotting in an extracorporeal blood circuit, and hence, fail to describe any dosages which would be necessary for such prevention, the invention of Claims 11-18 would not have been obvious to a person of ordinary skill in the art at the time the invention was made. Accordingly, the rejection of Claims 11-18 under 35 U.S.C. §103(a) based on said references is believed to be unwarranted and should be withdrawn

As to new Claims 19-26, nothing in the Petitou et al. disclosure describes the administration of the synthetic oligosaccharides of the invention via an external source, such as the herein claimed extracorporeal blood circuits, nor does Petitou et al. suggest a possible dosage for such external

administration. Moreover, neither Ahmad et al. nor Kudo et al. discloses the administration of a synthetic oligosaccharide to an extracorporeal blood circuit, and, thus, cannot possibly teach or suggest the claimed dosages for such administration. Accordingly, Ahmad et al. and Kudo et al. add nothing to Petitou et al., and the cited references taken either individually or in combination are incompetent to teach or suggest Claims 19-26.

In view of the foregoing amendments and remarks, it is submitted that the rejections under 35 U.S.C. § 112 and 35 U.S.C. § 103(a) have been overcome. Accordingly, reconsideration and withdrawal of the rejections of Claims 11-18 and allowance of Claims 11-26 are respectfully requested.

Respectfully submitted,

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